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Review

FIBROUS DYSPLASIA

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A B S T R A C T

Fibrous dysplasia provides the orthopedic surgeon with tremendous reconstructive challenges. The manifestations of the condition are very diverse and often involve organ systems not routinely cared for by the orthopedic surgeon. We present a concise review of the radiography, histology, clinical manifestations, and complications of this condition, with the main focus on the non-orthopedic management challenges.

In 1937, Albright et al[1] formally characterized a bone disorder that had been observed in sporatic cases in the literature. Albright et al reported five patients with the bone disorder and included 14 similar cases from the literature. Roentgen examination of several patients revealed skeletal abnormalities that were sporadic in distribution. Multiple, predominantly unilateral bone lesions appeared locally in digits and extremities. Albright observed granular areas of increased density that often obliterated the medullary canal. In such areas, the cortex was thin but intact in the absence of fracture. Abnormal bone appeared in one case due to the projection of islands of cartilage into the diaphysis of the bone. Albright recognized one of the "cardinal features" of the disease as a patchy skin pigmentation tending to be located on one side of the body. Albright reported that the depositions of melanin were proportional to the involvement of the skeletal disease. Albright also noted that in females, precocious puberty accompanied the disease. Although Albright could not explain the etiology of the precocious puberty, he suggested that a disturbance of the anterior pituitary gland affected the release of follicle stimulating hormone (FSH) causing premature development of secondary sexual characteristics.

In 1938, Lichtenstein[2] termed this clinical entity "fibrous dysplasia." In 1942, Lichtenstein and Jaffe[3] reviewed many previously published cases of fibrous dysplasia and added 15 of their own, thus establishing fibrous dysplasia as a distinct clinical and pathologic entity.

Fibrous dysplasia may manifest itself in three forms. In the monostotic form, only one bone is involved, and often patients are asymptomatic. Patients may undergo radiologic studies for unrelated reasons which reveal lytic areas characteristic of fibrous dysplasia. The symptomatic, monostotic patient may complain of pain, tenderness, or swelling in the involved area of bone. Monostotic patients may also present with pathologic fracture. The monostotic form is variously reported to be between 2.5 and 6 times more prevalent than the polyostotic form.[4-6] In monostotic fibrous dysplasia, the ribs, the proximal femurs, and craniofacial bones represent the majority of bone lesions. In the polyostotic form, multiple bones are involved. In polyostotic fibrous dysplasia, up to 75% of the skeleton may be involved; 85% of these patients sustain at least one pathologic fracture.[6] Within the first decade of life, the usual patient presents with leg pain, limp, or pathologic fracture. McCune-Albright syndrome is the third variation of fibrous dysplasia. The bone lesions are multiple and have a tendency to be unilateral in distribution. Often, the lesions cause expansion, weakness, and deformity in the cortex of the bones involved. Cafe au lait spots tend to appear on the side of the body in which the bone lesions occur. These brown pigmentations are variable in size with irregular margins. The outline of the pigment has been compared to the irregular appearance of the coast of Maine, as opposed to the smooth border ("coast of California") seen with the cafe au lait spots associated with neurofibromatosis.[7] Most often, the cafe au lait spots appear on the back of the neck, the lower lumbar

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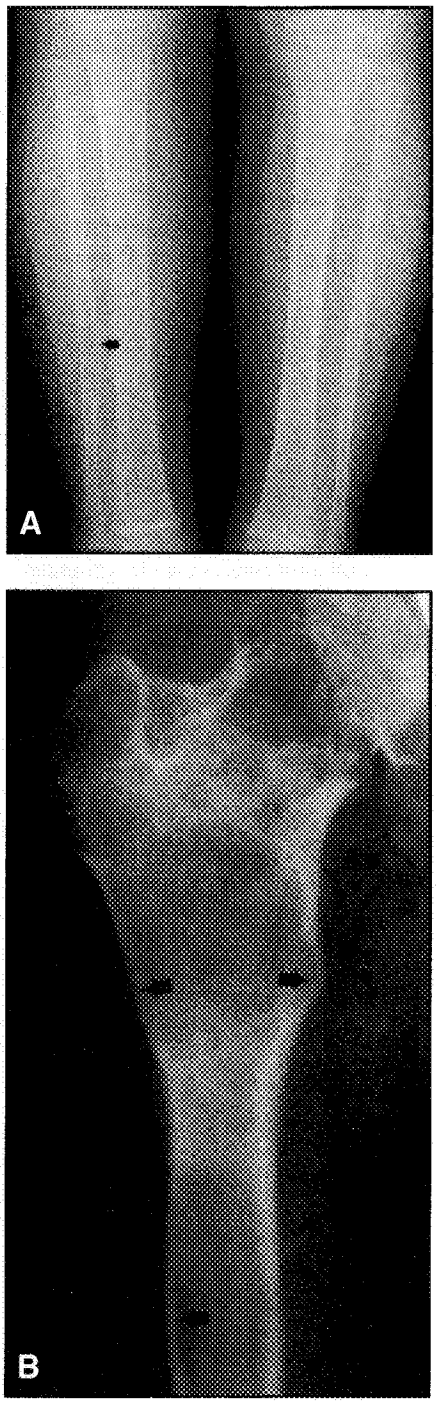


Fig 1. Expanded area of fibula with endosteal scalloping and typical "ground glass" matix (A). Upper femur showing typical scalloping of endosteal surfaces (B).

region, the face, the lips, and the oral mucosa.[8] Endocrine dysfunction is most often associated with this form of fibrous dysplasia. Such dysfunction may take the form of precocious puberty, hyperthyroidism, acromegaly, Cushing's disease, hyperparathyroidism, and diabetes mellitus. (Albright specified that precocious puberty may accompany fibrous dysplasia in females. However, it is known that precocious puberty may develop in males, and that multiple endocrinopathies may also present themselves.) Typically these patients have a more severe form of polyostotic bone involvement. Females may present with vaginal bleeding, due to precocious puberty, as early as the first few months after birth.

Fibrous dysplasia is not genetically inherited. Lemli in 1977[9] reported a case of monozygotic twin sisters with fibrous dysplasia. One twin was observed to have the classic signs of the McCune-Albright syndrome, including precocious puberty. The other twin had only bone manifestations. The observation that different phenotypes were produced from identical genotypes led Lemli to propose that a genetic mutation had occurred prior to birth. Happle,[10] however, postulated that the clinical syndrome was best explained by a mosaic pattern of gene mutation occurring early in embryogenesis but after fertilization. He postulated that a germ line mutation which would affect all cells in the embryo would have such profound expression as to be lethal. Weinstein et al[11-13] have published extensively on the genetic aspects of the syndrome. They have detected a mutation occurring in the gene for the alpha stimulatory subunit of the G protein, which is responsible for cyclic adenosine monophosphate (cAMP) formation.[13] They demostrated by micro-dissection techniques that abnormal appearing areas of endocrine tissue contained much higher amounts of the mutated G-protein, while those areas appearing most normal held barely detectable levels of the abnormal protein.[13] They were also able to detect gene mutations in non-endocrine tissues associated with liver and heart disease.[11] This gives more support to Happle's suggestion that gene mutation earlier in the process of embryogenesis may lead to such profound dysfunction that viability is altered.

RADIOGRAPHIC APPEARANCE

Upon radiographic examination, lesions of fibrous dysplasia may appear relatively lucent. However, a fibro-osseous matrix does exist which occasionally may include regions of fluid-filled cavities.[6] The focal thinning of the cortex is responsible for the ambiguity in differentiating lesions of fibrous dysplasia from cysts (ie, unicameral bone cyst). Expansion of the lesions within the medullary canal and endosteal resorption cause variations in thickness of the cortex. Although the lesions of fibrous dysplasia are most often unicameral, radiographically the lesions may appear multiloculated due to uneven erosion of the endosteal surface.[6] Segments of preserved cortex are situated between areas of cortical erosion that are responsible for the scalloped pattern associated with fibrous dysplasia (Fig 1).[6] The fibrous dysplasia matrix contains tightly meshed spicules within woven bone. The radiographic density of a lesion is determined by the quantity of woven bone present and to the extent that it has been mineralized. This produces a matrix density on radiographs that has been described as resembling ground glass. A thickened portion of sclerotic bone may surround the lesions.[6] Radiographic studies may reveal small islands of cartilage that develop in the bone lesions (Fig 2).

HISTOLOGIC APPEARANCE

Histologically, the bone lesions consist of small, irregular-shaped bone trabeculae within a collagenous fiber matrix. It appears that maturation of the primitive fibrous stroma is arrested at the early woven bone stage of skeletal differentiation. This poorly mineralized and immature fibrous tissue progressively replaces normal mineralized bone by a process of metaplasia.[14,15] Natural maturation of fibro-osseous tissue (ie, fracture callous) is characterized by replacement of immature woven bone by lamellar bone. However, lamellar replacement and osteoblastic rimming of trabeculae does not occur in fibrous dysplasia. The trabeculae often assume an irregular shape similar to "Chinese letters." From the ill-defined trabeculae to the

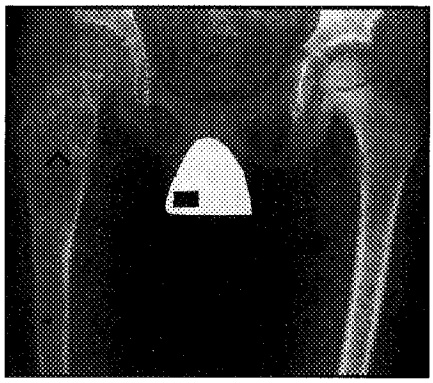
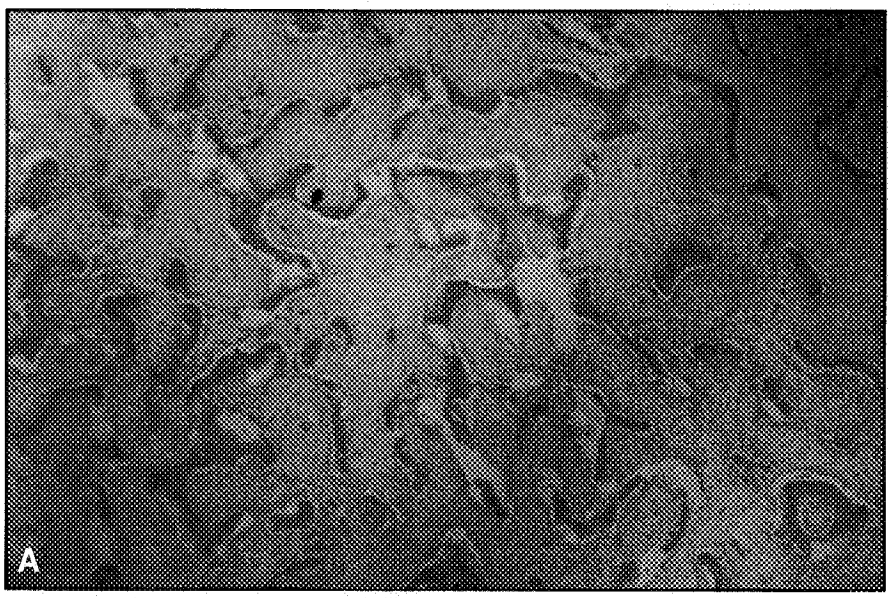


Fig 2. Upper femur demonstrates the chondrogenic areas (open arrow) and more typical fibrous area (closed arrow).

adjacent stroma, bone matrix may stream out along the collagen fibers (Fig 3A). As proliferation of the fibrous matrix continues, bone involvement can assume three forms: extension of existing lesions, appearance of new lesions, and increasing deformity of the involved bones.[6] Chondrogenic areas are often found in typical cases of fibrous dysplasia (Fig 3B). Calcification and endochondral bone formation may occur in the islands of cartilage, resulting in small, dense sections of calcification. The occurrence of endochondral bone formation in fibrous dysplasia patients is referred to as "fibrocartilaginous dysplasia" and most often manifests itself in the proximal femurs.[16] Biopsy of a primarily chondrogenic area may lead to confusion and difficulty in reaching an accurate diagnosis. A generous biopsy should be taken to help assure that representative areas of fibro-osseous tissue are obtained. Probably through a process of degeneration, expansile cystic areas may occur.[17] These areas are best characterized as an aneurysmal bone cyst as they contain lining cells characteristic of that entity. The fluid within the cyst may be either bloody or clear.

Differential Diagnosis

Differentiating fibrous dysplasia from similar bone lesions may be troublesome. Trauma to a weakened area of bone may lead to an inaccurate diagnosis, both histologically and radiographically. Fracture or surgery may lead to formation of whorled, fibrous tissue



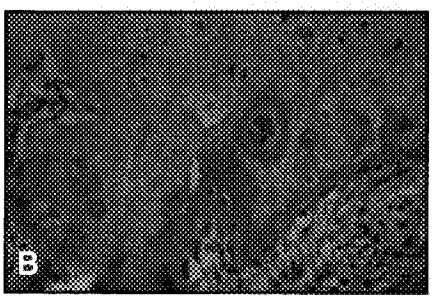


Fig 3. Typical histologic pattern of fibrous dysplasia (A). "Chondrogenic" fibrous dysplasia (B).

and focal lamellar bone formation not normally seen in untraumatized fibrous dysplasia. Secondary change may alter the apparent histology of fibrous dysplasia in specific areas. Non-specific, secondary changes may include cysts, whorling, stromal hemorrhages, zones of dense fibrosis, rimming of trabeculae by osteoblasts with lamellar transformation of woven bone, and possibly islands of cartilage. The term "traumatic dysplasia" was coined by Johnson[18] to specify such secondary, histologic alterations. Trauma to a region of fibrous dysplasia in a long bone may disguise evidence that supports a diagnosis of fibrous dysplasia.[15] In this case, a biopsy may reveal histologic criteria inconsistent with that of fibrous dysplasia. Both a careful history and review of the radiographs should be undertaken to elicit any evidence of superimposed trauma upon the underlying lesion. Careful consultation with the pathologist prior to biopsy is essential.

The lesion most often mistaken for fibrous dysplasia histologically is ossifying fibroma.[15] The confusion arises because ossifying fibromas are composed predominantly of fibrous tissue, and the bone trabeculae are composed of woven bone. However, the osteoblasts of ossifying fibromas typically rim the bone trabeculae in an orderly fashion, which distinguishes ossifying fibromas from the random placement seen in fibrous dysplasia. In addition, the osteoblasts of ossifying fibromas often deposit a surface layer of lamellar osteoid, further differentiating ossifying fibromas from fibrous dysplasia. Another source of confusion is radiographically differentiating fibrous dysplasia from unicameral bone cysts. A good quality radiograph will almost always reveal a matrix pattern in fibrous dysplasia, whereas the unicameral bone cyst is completely lucent. Fortunately, it is rare that the fiber pattern of bone spicules in the wall of a cyst cease to mature at the woven bone stage (a specific criteria of fibrous dysplasia). When this does occur, it may be difficult to microscopically differentiate a cyst from fibrous dysplasia.

Skeletal Manifestations

Fibrous dysplasia is associated with a multitude of skeletal complications. The fibrous matrix weakens the bone

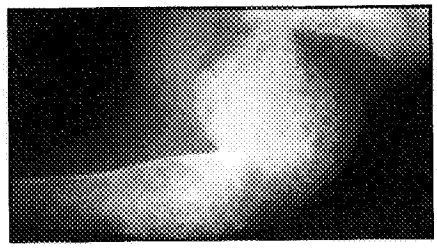


Fig 4. Typical shepherd's crook deformity.

and often leads to fracture. Multiple fractures are expected in children with fibrous dysplasia. Although normal healing of the subperiosteal bone occurs after fracture, fibrous lesions interfere with proper endosteal healing. Therefore, further fracture may be expected. Proliferation of the fibrous tissue may lead to numerous skeletal deformities. Gross involvement results in abnormally large bones. Leg-length discrepancy comprises 70% of physical deformities.[6] Fibrous dysplasia may lead to abnormal development of the proximal femur, causing a varus deformity—termed shepherd's crook deformity (Fig 4). Shepherd's crook deformity may be responsible for shortening of the involved bone, limp, and fatigue fractures resulting in disabling pain.[19] Nakashima et al[20] reported no cases of shepherd's crook deformity in monostotic patients. Tibial bowing and coxa vara may result from stresses of normal weight bearing imparted on fibrous dysplastic bones. Arthritis may develop in areas where fibrous lesions have distorted supporting structures of joint cartilage. Children with the McCune-Albright syndrome may experience rapid skeletal growth due to endocrine abnormalities. They are often much taller than their peers. Under the influence of precocious puberty, however, the physes tend to close prematurely, resulting in a person whose adult height is less than average at skeletal maturity.

Fibrous dysplasia may manifest itself in the skull causing gross deformity of the bones involved, and often further complications arise. Normally the lesions tend to be located on one side of the skull, producing marked asymmetry. Traction or direct compression of the optic nerve in fibrous dysplastic patients may cause loss of visual acuity.[21,22] Patients with spheroid involvement may experience narrowing of the optic canal resulting in visual loss.[21,22] Som et al[17] reported a case of an aneurysmal bone cyst in the paranasal sinuses of a 49-year-old woman. The aneurysmal bone cyst occurred in association with fibrous dysplasia. The patient suffered from respiratory problems (nasal), headaches, diplopia, and anosmia. Firat and Stutzman[23] reported two cases with deformity of the skull, increased density at the base, thickening of the occiput, and obliteration of the frontal sinuses.

ENDOCRINE MANIFESTATIONS

Multiple endocrine complications associated with fibrous dysplasia (McCune-Albright syndrome) have been described.[11,24-30] There is no general agreement as to the relationship between the abnormal histology of the fibrous dysplasia and the endocrinopathies. Altered histology and hyperfunction of several endocrine glands and associated organs result in the following conditions which may be seen in the McCune-Albright syndrome:

Precocious puberty is seen most often and may present itself in males, but is most often recognized in females. The unexpected onset of menstruation in young girls may be most traumatic. Females with the McCune-Albright syndrome demonstrate lower than average levels of gonadotropins as compared to normal prepubertal girls. Also, the anterior pituitary shows little response to luteinizing-releasing hormone (LHRH). Thus, Feuillan et al[27] concluded that the precocious puberty was not dependent on the hypothalamus/anterior pituitary axis. Feuillan et al postulated that hyperfunction of the ovaries may stimulate an increase in estrogen biosynthesis resulting in the release of estradiol from the ovaries.

Hyperthyroidism is characterized by an increased metabolic rate, weight loss, muscular weakness, and irritability.[26] Hyperthyroidism in McCune-Albright patients demonstrates no sexual preference as seen in patients with Grave's disease.[26]

Acromegaly is caused by oversecretion of growth hormones from the pituitary gland after maturity. Enlargement of the extremities characterizes the condition. Chung et al[24] reported a case of a 17-year-old girl with acromegaly. It was suggested that she suffered from a "growth hormone-secreting pituitary tumor" brought on by hypothalamic stimulation. Similarly, Premawardhana et al[31] reported a case of a 26-year-old woman with acromegaly resulting from a pituitary adenoma.

Cushing's syndrome results from the hypersecretion of corticosteroids due to tumors of the adrenal cortex or oversecretion of adrenocorticotropic hormone from the anterior pituitary. Danon and Crawford[26] recognized growth failure, hirsutism, poor motor development, and muscle weakness in infants. Adolescents were afflicted with hypertension, acne, cutaneous striae, truncal obesity, and muscle wasting. Osteoporosis and coarse trabeculation of bone were found radiographically in addition to fibrous lesions.

Hyperparathyroidism is characterized by alterations in functions of bone cells (osteoporosis), renal tubules (kidney stones and calcium deposits), and gastrointestinal mucosa (anorexia, nausea, vomiting, and abdominal pains). Before 1987, Danon and Crawford[26] noted that only three cases of hyperparathyroidism had been reported in the McCune-Albright syndrome.

In addition to the preceding endocrinopathies, cases of hyperprolactinemia and diabetes mellitus have been reported in McCune-Albright patients.[24,25] Women with fibrous dysplasia should be made aware that bone lesions may change during pregnancy. Stevens-Simon et al[32] reported on a 17-year-old girl with fibrous dysplasia who became pregnant. The patient experienced painless swellings in her skull. She had been evaluated for similar swellings when she was 4 years old. Apparently, hormonal changes due to pregnancy may result in exacerbation of the bone lesions. It has been suggested that estrogen and progesterone may influence the regulation of bone growth and metabolism. Pensler et al[30] speculated that an increase in nuclear sex steroid hormone receptors in fibrous dysplasia may facilitate the binding of estrogen and progesterone, resulting in localized changes in bone metabolism. Therefore, one may conclude that an increase in sex steroid

hormones during pregnancy may result in overgrowth of osteogenic cells in fibrous dysplastic lesions. This may have implications for the choice of contraceptives in these patients.[33]

TREATMENT

In treating fibrous dysplasia, surgery should be considered in the context of progressive deformity, nonunion of fractures, and persistent pain from mechanical insufficiency. Surgery is often complicated by the fibrous nature of the lesions. The uncalcified matrix in fibrous dysplastic patients does not provide for a firm foundation in which to anchor internal fixation devices.[6,19,34,35] Problems in polyostotic patients are compounded, as fibrous dysplasia may manifest itself in bone that would normally be the appropriate choice from which to extract a bone graft. If circumstances allow for an autogenous bone graft, the physician should utilize a graft that is primarily cortical. Fibrous dysplasia material may be transplanted into an originally unaffected region of bone. Therefore, sterile equipment, separate drapes, gowns, and gloves should be used to obtain the autogenous graft. Fibrous dysplasia tends to rapidly resorb cancellous bone grafts, resulting in recurrence of symptoms. Autogenous cortical grafts undergo partial resorption; however, the interstitial lamellae remain indefinitely and provide structural support. Enneking and Gearen[19] proposed that autogenous cortical grafts were most effective when treating fatigue fractures, preventing additional fractures, and treating deformation of the proximal femur without aggressive en bloc excision. Their patients generally did not demonstrate the profound degree of deformity seen in the more severe cases of McCune-Albright syndrome.

Patients with proximal femur involvement normally present with fibrous lesions in the femoral neck and intertrochanteric regions. Cortical graft should be continuous between the noninvolved femoral head and lateral cortex in the subtrochanteric region. This provides firm anchorage at both ends of the graft. Enneking and Gearen[19] compared reports of grafting previously published by Harris et al[6] and Stewart et al.[36] In the combined series, Enneking and Gearen[19] reported that 13 of the 25 cancellous grafts were failures; however, 13 of their 15 cases that involved autogenous cortical grafts were successes. Success rates were based on the relief of pain, union of fracture, and prevention of further deformity. Significant progressive deformity of the femoral neck and recurrent deformity following grafting often require more aggressive techniques. Internal fixation may be employed once shepherd's crook deformity and coxa vara develop; however, very poor bone stock makes the choice of implant difficult. The dysplastic lesion is curetted, filled with the graft, and the support mechanism of choice is implanted. Shepherd's crook deformity may be best treated by aggressive resection of the deformed upper femur with medial displacement of the remaining femoral shaft to recreate valgus. In severe cases of deformity that follow multiple previous surgical reconstructions, extensive allografting of the long bone segments may be justified as a salvage procedure (Fig 5). Endoprosthetic replacement also may be appropriate in selected cases.[37]

Assessing the age of the patient and location of the lesion are important in determining the strategy for treatment of fibrous dysplasia. Stephenson et al[38] reported that lesions in the upper extremity responded well (88%) to closed forms of treatment regardless of the age of the patient. Closed treatment or curettage and bone grafting in the lower extremity of patients 18 years or older showed satisfactory results (88%). However, the resorption of the graft in lower extremities of patients less than 18 years of age leads to unsatisfactory results (81%). Patients less than 18 years of age with lesions in the lower extremity responded with greatest results (86%) to internal fixation.[38] Strassburger et al[39] concluded that only small, solitary lesions responded well to curettage and bone grafting.

Surgical correction of asymmetry and deformation of the skull is usually successful. However, 25% of patients require subsequent surgery to reduce further bony enlargement. The removal of dysplastic lesions followed by implantation of autogenous bone graft has shown some success in preventing the recurrence of gross bony overgrowth.

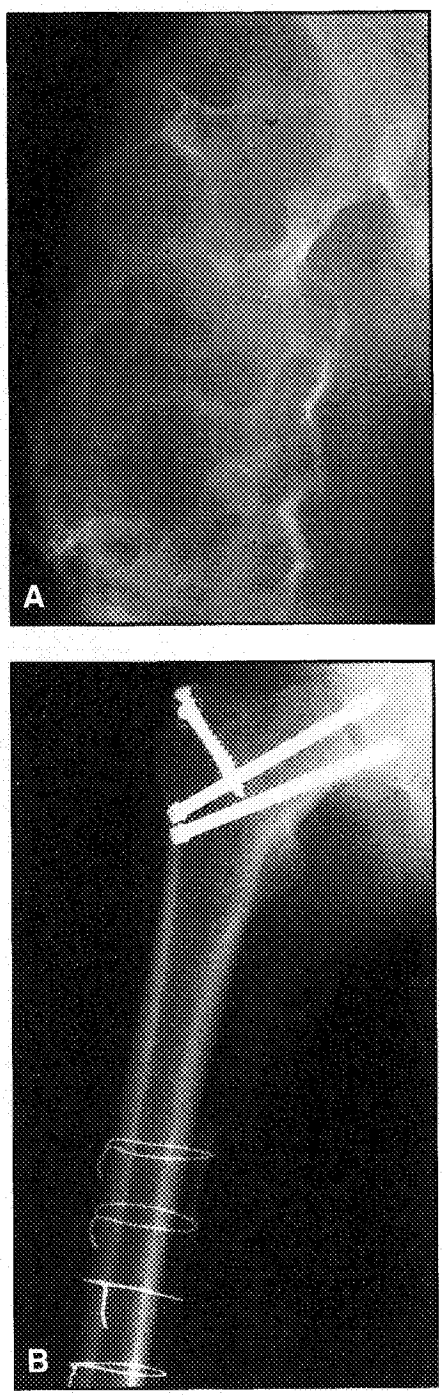


Fig 5. Upper femur showing extensive involvement with fibrous dysplasia and aneurysmal bone cyst (A). Reconstruction utilizing allograft (B).

The resorptive nature of fibrous dysplasia has prompted physicians to test the effects of antiresorptive compounds

in lesions of fibrous dysplasia. Liens et al[40] reported success in the administration of intravenous pamidronate in treating nine patients (14 lesions) with fibrous dysplasia. They treated eight polyostotic cases and one monostotic case. The patients were 13 to 59 years of age and were followed for 18 to 48 months. Decreased pain was noted in all lesions and complete disappearance of pain in 12 of 14 sites. Osteolytic areas in four patients underwent progressive refilling, and reduction in the size of a lesion was seen in four other patients. Liens et al[40] caution that younger patients with more symptomatic involvement of fibrous dysplasia should be observed intently due to the potentially adverse effects of pamidronate on mineralization at the physis.

Cryotherapy, as an adjunct to surgical treatment of fibrous dysplasia, had been reported by Marcove.[41] Curettage of the lesion preceded application of liquid nitrogen. No recurrence of the disease was observed in seven patients treated with cryotherapy. The specifics of each lesion were not reported. Presumably, these represented monostotic disease.

Fibrous dysplasia rarely undergoes malignant transformation (0.5%); however, radiation treatment may increase those odds 400 times.[42] In monostotic patients, the facial bones and skull are most likely to incur malignant change. Malignant transformation in polyostotic patients most often occurs in the femur. Involvement of the craniofacial bones, humerus, pelvis, tibia, and fibula occurs as well.[43-45] Osteosarcomas most often represent the malignant change that may occur in fibrous dysplastic patients, but cases of fibrosarcoma and chondrosarcoma have been reported. Radiotherapy should be condemned as a primary means to treat fibrous dysplasia. Its poor results and enhancement of malignant transformation should encourage physicians to utilize other modalities.

Treating the endocrine manifestations associated with fibrous dysplasia often involves hormonal or surgical intervention. The aromatase inhibitor testolactone has been used to decrease estrogen levels in females with precocious puberty. Feuillan et al[27] reported reduction in growth rates in three of their five patients afflicted with precocious puberty. Menstrual periods stopped in three of four girls with regular menses. Lawless et al[29] emphasized the importance of understanding a patient's vulnerability to thyroid disorder. They reported a case of an 8-year-old boy with McCune-Albright syndrome who underwent femoral and tibial osteotomies. Postoperatively, the boy developed thyroid storm. Premawardhana et al[31] proposed the combination of radiotherapy and a somatostatin analogue to treat acromegaly in McCune-Albright patients. Pituitary surgery in patients with the McCune-Albright syndrome often presents technical difficulties. Surgical removal of the hyperplastic adrenal glands is the preferred treatment of Cushing's syndrome in McCune-Albright patients. Hyperparathyroidism is most often treated by removal of one or all of the parathyroids.

SUMMARY

Fibrous dysplasia is characterized by unilateral bone lesions, and in the McCune-Albright Syndrome, cafe au lait pigmentation, and endocrine dysfunction. No cases of inheritance have been reported. The physician should consult with a pathologist prior to biopsy, extract generous biopsies, and review quality radiographs. Fibrous dysplasia may present histologic characteristics similar to other bone diseases. However, a meticulous examination will reveal a combination of criteria unique to fibrous dysplasia.

The etiology of fibrous dysplasia remains unclear. Treatment is therefore directed at controlling the disease—not preventing it. Physicians may surgically provide patients with temporary relief of pain and deformity; however, further proliferation of the fibrous tissue is expected. Surgical management should be directed at treating early, mild deformity, as severe deformity is very difficult to reverse. Cortical grafts are far superior to cancellous grafts and should be used whenever possible. An endocrinologist should be consulted in cases of endocrine manifestations. The endocrinologist is best qualified to address the endocrine hyperfunction that may ensue during or after surgery. If measures are to be taken to prevent problems associated with fibrous dysplasia, the course of research will most likely involve biochemically directed efforts.

REFERENCES

1. Albright F, Butler AM, Hampton AO, Smith P. Syndrome characterized by osteitis fibrosa disseminate, areas of pigmentation and endocrine dysfunction with precocious puberty in females; report of 5 cases. *N Engl J Med.* 1937; 216:727-746.

2. Lichtenstein L. Polyostotic fibrous dysplasia. *Arch Surg.* 1938; 36: 874-898.

3. Lichtenstein L, Jaffe HL. Fibrous dysplasia of bone; a condition affecting one, several or many bones, graver cases of which may present abnormal pigmentation of skin, premature sexual development, hyperthyroidism or still other extraskeletal abnormalities. *Arch Pathol.* 1942; 33:777-816.

4. Mirra JM, Gold RH. Fibrous dysplasia. In Mirra JM, Piero P, Gold RH, eds. *Bone Tumors.* Philadelphia, Pa: Lea & Febiger; 1989:191-226.

5. Wilner D. Fibrous dysplasia of bone. In Wilner D, ed. *Radiology of Bone Tumors and Allied Disorders.* Philadelphia, Pa: WB Saunders; 1982:1443-1580.

6. Harris WH, Dudley HR Jr, Barry RJ. The natural history of fibrous dysplasia. An orthopaedic, pathological and roentgenographic study. *J Bone Joint Surg.* 1962; 44A:207-233.

7. Rosenberg RN, Sassin J, Zimmerman EA, Carter S. The interrelationship of neurofibromatosis and fibrous dysplasia. *Arch Neurol.* 1967; 17:174-179.

8. Benedict PH, Szabo G, Fitzpatick TB, Sinsei SJ. Melanotic macules in Albright's syndrome and in neurofibromatosis. *JAMA.* 1968; 205:618-626.

9. Lemli L. Fibrous dysplasia of bone. Report of female monozygotic twins with and without the McCune-Albright syndrome. *J Pediatr.* 1977; 91:947-949.

10. Happle R. The McCune-Albright syndrome: a lethel gene surviving by mosaicism. *Clin Genet.* 1986; 29:321-324.

11. Shenker A, Weinstein LS, Moran A, et al. Severe endocrine and nonendocrine manifestations of the McCune-Albright syndrome associated with activating mutations of stimulatory G protein GS. *J Pediatr.* 1993; 123:509-518.

12. Weinstein LS, Shenker A. G Protein mutations in human disease. *Clin Biochem.* 1993; 26:333-338.

13. Weinstein LS, Shenker A, GeJman PV, Merino MJ, Friedman E, Spiegel AM. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. *N Engl J Med.* 1991; 325:1688-1695.

14. Mandell GA, Harcke HT, Kumar SJ. Fibrous lesions of the extremities. *Topics Magn Reson Imaging.* 1991;4:45-55.

15. Reed RJ. Fibrous dysplasia of bone. A review of 25 cases. *Arch Path.* 1963; 75:480-495.

16. Kransdorf MJ, Moser RP Jr, Gilkey FW. Fibrous dysplasia. *Radiographics.* 1990; 10:519-537.

17. Som PM, Schatz CJ, Flaum KG, Lanman TH. Aneurysmal bone cyst of the paranasal

sinuses associated with fibrous dysplasia: CT and MR findings. *J Comput Assist Tomogr.* 1991; 15:513-515.

18. Johnson LC. *Proceedings of seminar of South-Eastern and South-Central Regions, College of American Pathologists.* 1952; Nov:12-13.

19. Enneking WF, Gearen PF. Fibrous dysplasia of the femoral neck. Treatment by cortical bone grafting. *J Bone Joint Surg.* 1986; 68A:1415-1422.

20. Nakashima Y, Kotoura Y, Nagashima T, Yamamuro T, Hamashima Y. Monostotic fibrous dysplasia of the femoral neck. A clinicopathologic study. *Clin Orthop.* 1984; 191:242-248.

21. Bland LI, Marchese MJ, McDonald JV. Acute monocular blindness secondary to fibrous dysplasia of the skull: a case report. *Ann Ophthalmol.* 1992; 24:263-266.

22. Weisman JS, Helper RS, Vinters HV. Reversible visual loss caused by fibrous dysplasia. *Am J Ophthalmol.* 1990; 110:2244-2249.

23. Firat D, Stutzman L. Fibrous dysplasia of the bone. Review of twenty-four cases. *Am J Med.* 1968; 44:421-429.

24. Chung KF, Alaghband-Zadeh J, Guz A. Acromegaly and hyperprolactinemia in McCune-Albright syndrome. Evidence of hypothalamic dysfunction. *Am J Dis Child.* 1983; 137:134-136.

25. Cuttler L, Jackson JA, Saced uz-Zafar M, Levitsky LL, Mellinger RC, Frohman LA. Hypersecretion of growth hormone and prolactin in McCune-Albright syndrome. *J Clin Endocrinol Metab.* 1989; 68:1148-1154.

26. Danon M, Crawford JD. The McCune-Albright syndrome. *Ergeb Inn Med Kinderheilk.* 1987; 55:81-115.

27. Feuillan PP, Foster CM, Pescovitz OH, et al. Treatment of precocious puberty in the McCune-Albright syndrome with the aromatase inhibitor testolactone. *N Engl J Med.* 1986; 315:1115-1119.

28. Freedman HJ. Disturbances of function of the suprarenal glands in children. *Am J Dis Child.* 1932; 44:1285-1292.

29. Lawless ST, Reeves G, Bowen JR. The development of thyroid storm in a child with McCune-Albright syndrome after orthopaedic surgery. *Am J Dis Child.* 1992; 146:1099-1102.

30. Pensler JM, Langman CB, Radosevich JA, et al. Sex steroid hormone receptors in normal and dysplastic bone disorders in children. *J Bone Miner Res.* 1990; 5:493-498.

31. Premawardhana LD, Vora JP, Mills R, Scanlon MF. Acromegaly and its treatment in the McCune-Albright syndrome. *Clin Endrocrinol.* 1992; 36:605-608.

32. Stevens-Simon C, Stewart J, Nakashima II, White M. Exacerbation of fibrous dysplasia associated with an adolescent pregnancy. *J Adolesc Health.* 1991; 12:403-405.

33. Maccari S, Fornaciari G, Bassi C, Beltrami M, Tinterri N, Plancher AC. Contraceptive methods in the McCune-Albright syndrome. *Clin Exper Obstet Gynecol.* 1989; 16:129-130.

34. Freeman BH, Bray EW III, Meyer LC. Multiple osteotomies with Zickel nail fixation for polyostotic fibrous dysplasia involving the proximal part of the femur. *J Bone Joint Surg.* 1987; 69A:691-698.

35. DePalma AF, Dodd PM. Reconstructive surgery in fibrous dysplasia of bone. *Clin Orthop.* 1961; 19:132-147.

36. Stewart MJ, Gilmer WS, Edmondson AS. Fibrous dysplasia of bone. *J Bone Joint Surg.* 1962; 44B:302-318.

37. Present DA, Kuschner SH. Total femur replacement. *Clin. Orthop.* 1990; 251:166-167.

38. Stephenson RB, London MD, Hankin FM, Kaufer H. Fibrous dysplasia—an analysis of options for treatment. *J Bone Joint Surg.* 1987; 69A:400-409.

39. Strassburger P, Garber CZ, Hallock H. Fibrous dysplasia of bone. *J Bone Joint Surg.* 1951; 33A:407-420.

40. Liens D, Delmas PD, Meunier PJ. Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. *Lancet.* 1994; 343:953-954.

41. Marcove RC. A 17-year review of cryosurgery in the treatment of bone tumors. *Clin Orthop.* 1982; 163:231-234.

42. Edgerton MT, Persing JA, Jane JA. The surgical treatment of fibrous dysplasia. With emphasis on recent contributions from craniomaxillofacial surgery. *Ann Surg.* 1985; 202: 459-479.

43. Ishida, T, Machinami R, Kojima T, Kikuchi F. Malignant fibrous histiocytoma and osteosarcoma in association with fibrous dysplasia of bone. Report of three cases. *Path Res Prac.* 1992; 188: 757-763.

44. Latham PD, Athanasou NA, Woods CG. Fibrous dysplasia with locally aggressive malignant change. *Arch Orthop Trauma Surg.* 1992; 111:183-186.

45. Chetty R, Kalan MR, Kranold DH. Malignant transformation in fibrous dysplasia. A report of 3 cases. *South Afr J Surg.* 1990; 28:80-82.